Q19214US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

HIROYUKI MIYACHI ET AL : EXAMINER: ANDERSON, R. L.

SERIAL NO: 10/049,645 :

FILED: FEBRUARY 25, 2002 : GROUP ART UNIT: 1626

FOR: SUBSTITUTED BENZYLTHIAZOLIDINE-2,4-DIONE DERIVATIVES

DECLARATION UNDER 37 C.F.R. §1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Now comes Koji Murakami who deposes and states:

1. That I am a graduate of Tokyo College of Pharmacy and received my Ph.D. degree in the year 2000.

2. That I have been employed by Kyorin Pharmaceutical Co., Ltd. for 16 years as a Researcher in the field of Pharmacology

3. That the following comparison was carried out by me or under my direct supervision and control.

4. That I am familiar with the present application, its prosecution history, the outstanding rejections over the cited references.

5. That I am familiar with the pending claims in the present application.

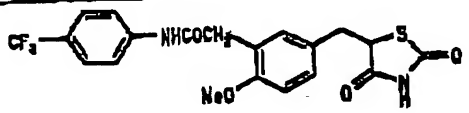
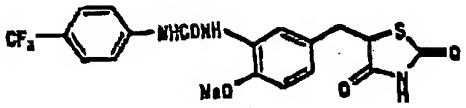
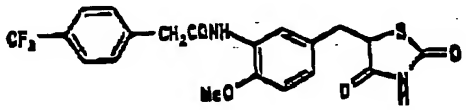
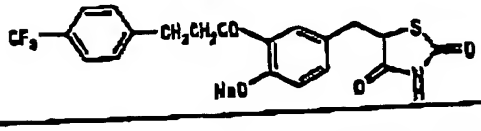
6. That I hereby state that the following remarks regarding procedure, result generation, and data interpretation is done so to the best of my knowledge in the related technical field and that I have read and understand all information herein.

The comparative experimental data, which are requested by the Examiner, have been prepared as described under.

The present invention submits the compound having agonist activity of human peroxisome proliferator-activated receptor (PPAR) and has been developed on the expectation of exhibiting lipid-lowering action based on agonist activity of PPAR alpha in addition of blood sugar-lowering action based on agonist activity of PPAR gamma. That is, the present invention has developed a dual agonist capable of activating PPAR alpha and gamma.

In Table 8 of the present specification, it is described that the Example compounds of the present invention show the strong transactivation to the both of PPAR alpha and gamma. The data of transactivation of the present compound are transferred from the specification as under.

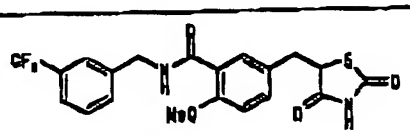
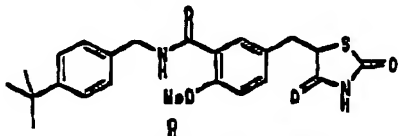
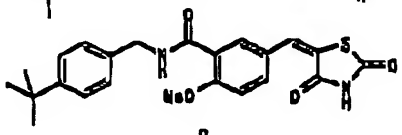
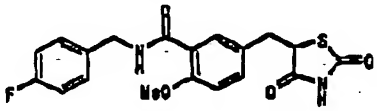
(Table A) Transactivation of the present compound

Example No.	Structure	Transactivation PPARα EC_{50} (μmol/L)	Transactivation PPARγ EC_{50} (μmol/L)
6		0. 60	3. 30
11		0. 55	0. 43
15		0. 86	1. 10
22		0. 80	0. 40

From this result, it is demonstrated that the compounds represented by bonding modes of four kinds defined for A in the general formula (1) of the present invention have the activation action to PPAR alpha and gamma.

Next, the tested result of the transactivation by the same experiment concerning Examples 17, 22, 23, 28 of the cited reference EP 0 846 693 is shown below (the data of Example 38 is also requested, but the data thereof could not be derived, because the amount of said sample was too small therefor).

(Table B) Transactivation of the cited reference compounds

Example No.	Structure	Transactivation PPARα EC_{50} (μmol/L)	Transactivation PPARγ EC_{50} (μmol/L)
17		>10	0.18
22		>10	0.23
23		>10	0.50
28		>10	0.20

As this result, the cited reference compounds, although strong in activation to PPAR gamma, are considered to be very weak in activation to PPAR alpha, because it is not recognized in the level of 10 micro·mol/L. The cited reference compounds are mainly the agonist of PPAR gamma.

On the other hand, it is obvious that the present invention compounds significantly have the activation to PPAR alpha at the same time in addition of the activation to PPAR gamma. The present invention compounds are the dual agonist having activating the both of PPAR alpha and gamma.

Accordingly, the present invention compounds are expected to exhibit lipid·lowering action based on PPAR alpha together with blood sugar·lowering action based on PPAR gamma.

3) Our comment

The present invention concerns the compound having agonist activity of human peroxisome proliferator·activated receptor (PPAR) and has developed a dual agonist which can activate PPAR alpha and gamma with expecting the manifestation of lipid·lowering action based on PPAR alpha agonist together with blood sugar·lowering action based on PPAR

gamma agonist.
Comparing the PPAR activation data of the cited reference with the activation data of the present invention, we can demonstrate the existence or the non-existence of PPAR alpha activity.
The present invention compounds which are strong in activating both of PPAR alpha and gamma are expected to exhibit the effect on the aspect of lowering function of lipid, which have the excellent characteristics in comparison with the cited reference compounds.

7. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

8. Further deponent saith not.

Koji Murakami
Signature

20/08/2003
Date